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Wesolowska, Karolina

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Is the Association Between Depressive Symptoms and Glucose Bidirectional? A Population-Based  
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Karolina Wesołowska, Marko Elovainio, Taina Hintsala, Markus Jokela, Laura Pulkki-Råback,  
Jari Lipsanen, Markus Juonala, Olli Raitakari, and Liisa Keltikangas-Järvinen

University of Helsinki

National Institute for Health and Welfare

University of Turku

Turku University Hospital

Murdoch Children's Research Institute

Author Note

Karolina Wesołowska, Taina Hintsala, Markus Jokela, Jari Lipsanen, and Liisa Keltikangas-Järvinen, Department of Psychology and Logopaedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland. Marko Elovainio, Department of Psychology and Logopaedics, Faculty of Medicine, University of Helsinki, Helsinki, Finland, and National Institute for Health and Welfare, Helsinki, Finland. Laura Pulkki-Råback, Department of Psychology and Logopaedics, Faculty of Medicine, and Helsinki Collegium for Advanced Studies, University of Helsinki, Helsinki, Finland. Markus Juonala, Department of Medicine, University of Turku, Turku, Finland, Division of Medicine, Turku University Hospital, Turku, Finland, and Murdoch Children's Research Institute, Parkville, Victoria, Australia. Olli Raitakari, Research Center of Applied and Preventive Cardiovascular Medicine,

University of Turku, Turku, Finland, and Department of Clinical Physiology and Nuclear Medicine, Turku University Hospital, Turku, Finland.

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Correspondence concerning this article should be addressed to Karolina Wesołowska, Department of Psychology and Logopedics, Faculty of Medicine, University of Helsinki, P.O. Box 9 (Siltavuorenpenger 1 A), 00014 Helsinki, Finland. E-mail: karolina.wesolowska@helsinki.fi

## Abstract

**Objective:** Depressive symptoms have been associated with Type 2 diabetes, but the temporal direction of this association and the underlying mechanisms remain unclear. The present study examined a potential, bidirectional association between depressive symptoms and glucose levels in women and men, and the factors mediating this association. **Methods:** The participants were from the Cardiovascular Risk in Young Finns Study, a prospective, population-based, cohort study ( $n = 2534$ ). Depressive symptoms were assessed using a modified Beck Depression Inventory. Fasting glucose was measured concurrently with depressive symptoms. To analyze the data, a multiple-group cross-lagged analysis and parallel multiple mediation in structural equation modeling were used. **Results:** Depressive symptoms in 2001 were positively associated with glucose levels in 2012 in women ( $\beta = .07, p = .023$ ) but not in men ( $\beta = -.03, p = .45$ ). This sex difference was statistically significant ( $p = .042$ ). Glucose levels in 2001 did not predict depressive symptoms in 2012 in either women or men ( $ps = .96$ ). Changes in body mass index, high-sensitivity C-reactive protein, alcohol consumption, or tobacco or cigarette smoking did not mediate the observed association ( $ps > .05$ ). **Conclusions:** The results showed a positive association between depressive symptoms and glucose levels in women but not in men. The direction of this relationship seems to be from depressive symptoms to glucose levels rather than the reverse. Changes in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking may not play a mediating role in this observed association.

**Keywords:** depressive symptoms, fasting glucose, hyperglycemia, sex differences, Type 2 diabetes mellitus

## Is the Association Between Depressive Symptoms and Glucose Bidirectional? A Population-Based Study

The prevalence of clinical depression (Nichols & Brown, 2003) and depressive symptoms has been shown to be higher in individuals with Type 2 diabetes compared with in the general population (Anderson, Freedland, Clouse, & Lustman, 2001). Despite the fact that the co-occurrence of symptoms of depression and Type 2 diabetes has attracted much research interest, the temporal direction of this association and the underlying mechanisms remain unclear (Tabák, Akbaraly, Batty, & Kivimäki, 2014). If depressive symptoms do increase the risk of Type 2 diabetes, or vice versa, the association between these two conditions should already be observed with metabolic changes that precede diabetes onset, such as elevated glucose concentrations. Thus, chronically increased glucose levels may be one of the plausible mechanisms that accounts for the reported, positive relationship between depressive symptoms and Type 2 diabetes.

Most previous research of the association between depressive symptoms and hyperglycemia has been based on cross-sectional data (Kivimäki et al., 2009; Mezuk et al., 2013; Nouwen et al., 2011), which cannot address the temporal direction of the association, whereas evidence from longitudinal studies (Akbaraly et al., 2013; Eriksson et al., 2008; Georgiades et al., 2007; Golden et al., 2008; Hamer, Batty, & Kivimäki, 2011) has provided inconsistent results. A Swedish prospective, population-based study (Eriksson et al., 2008) suggested that hyperglycemia might be a mechanism through which depressive symptoms could contribute to Type 2 diabetes development in men. These results were not supported by a quasi-experimental study, performed in a clinical sample of U.S. patients with diabetes (Georgiades et al., 2007), which reported that changes in depressive symptoms are not associated with changes in glycemia over a 1-year period. On the other hand, the English Longitudinal Study of Aging examining the role of poor glucose metabolism in the

development of depressive symptoms (Hamer et al., 2011) showed that hyperglycemia can be a causal risk factor for depressive mood, especially in men. Findings from the Whitehall II Study (Akbaraly et al., 2013) documented, however, no association between elevated glucose levels and subsequent depressive symptoms in either women or men. Similarly, the Multi-Ethnic Study of Atherosclerosis (Golden et al., 2008) also suggested that chronic hyperglycemia is unlikely to be a mechanism underlying the link between Type 2 diabetes and depressive symptoms.

Elevated glucose could lead to depressive symptoms through several pathways. First, chronic hyperglycemia has been shown to elicit such symptoms associated with negative mood as fatigue and difficulty with concentration (Adriaanse et al., 2005). Further, elevated glucose levels can influence the development of macrovascular and microvascular complications that may have biological effects which could, either individually or collectively, increase the risk of depressive symptoms (Egede, 2005). Another possible pathway is that higher glucose concentrations can activate pro-inflammatory mechanisms (Stuart & Baune, 2012) implicated in the reduction of neuroplasticity (Calabrese et al., 2014), which, in turn, has been associated with depression (Lee & Kim, 2010).

Plausible mechanisms through which depressive symptoms could directly influence hyperglycemia include biological alterations in the sympathetic nervous system (SNS) and the hypothalamic-pituitary-adrenal axis (HPA axis; Brown, Varghese, & McEwen, 2004; Krishnan & Nestler, 2008), and immune dysregulation and activation of the inflammatory response system (Esser, Legrand-Poels, Piette, Scheen, & Paquot, 2014; Kiecolt-Glaser, Derry, & Fagundes, 2015). These two mechanisms have not, however, consistently been linked to an increased risk of Type 2 diabetes (Tabák et al., 2014).

Depressive symptoms could also lead to elevated glucose levels indirectly by worsening adherence to healthy diet (Alhazmi, Stojanovski, McEvoy, & Garg, 2014; Lin et al., 2004) and physical activity (Jeon, Lokken, Hu, & van Dam, 2007; van Gool et al., 2003). Other possible pathways through which depressive symptoms could contribute to disturbed glycemia include excess body fat (Ganz et al., 2014; Luppino et al., 2010) and an increase in health-risk behaviors, such as alcohol consumption (Kao, Puddey, Boland, Watson, & Brancati, 2001; Wang & Patten, 2001) and smoking (Maddatu, Anderson-Baucum, & Evans-Molina, 2017; van Gool et al., 2003). So far, the effect of depressive symptoms on health behaviors and the impact of depression-related behaviors on the risk of Type 2 diabetes have only been examined in isolation in previous non-clinical studies. Thus, the mediating role of behavioral factors in the association between depressive symptoms and hyperglycemia remains uncertain.

Establishing the temporal ordering in the association between depressive symptoms and glucose levels, and the mechanisms underlying this relationship would provide valuable information on the nature of the association between depressive symptoms and Type 2 diabetes. Thus, the first aim of our prospective, population-based, cohort study was to investigate the direction of the association between depressive symptoms and glucose concentrations in women and men. This relationship was tested using three repeated measurements of depressive symptoms and fasting glucose (years: 2001, 2007, and 2012). The model with two repeated surveys (the time lapse of 11 years from 2001 to 2012) was the primary model, while the model with three time points (6- and 5-year time lag from 2001 to 2007 and from 2007 to 2012) was tested additionally. This was due to the fact that the potential association between depressive symptoms and glucose levels, or plausible sex differences in this relationship were more likely to be observed within a longer time lapse, given that our study was based on a relatively young population (before the peak age of the

onset for Type 2 diabetes). The second objective of the present study was to examine whether changes in body fat, inflammation, alcohol consumption, or tobacco or cigarette smoking mediate the association between depressive symptoms and glucose levels.

## **Methods**

### **Participants**

The participants were from the Cardiovascular Risk in Young Finns Study, an ongoing, prospective, population-based study, which has examined risk factors underlying cardiovascular diseases in the Finnish population (Raitakari et al., 2008). The study has been conducted in all Finnish cities with a medical school (Helsinki, Kuopio, Oulu, Tampere, and Turku) and their rural surroundings. A randomized sample of 3596 healthy Finnish children and adolescents (both boys and girls) aged 3, 6, 9, 12, 15, and 18 years has been followed since 1980 (the baseline study). Thereafter, eight follow-up studies have been performed in 1983, 1986, 1989, 1992, 1997, 2001, 2007, and 2012. The study was approved by the ethics committee of each of the five participating universities (i.e., University of Helsinki, University of Kuopio, University of Oulu, University of Tampere, and University of Turku). The participants' written informed consent was obtained.

The present study was based on the data from the 2001, 2007, and 2012 follow-ups. To be included in the first part of the statistical analysis, the participants had to have information on either depressive symptoms or glucose concentrations in 2001 or 2012, and information on socioeconomic status (SES) in 2001 ( $n = 2560$ ). Those individuals who in 2001 had Type 1 diabetes or Type 2 diabetes were excluded ( $n = 26$ ). Thus, the final sample consisted of 2534 participants (70.5% of the original sample).

In the second part of the statistical analysis (additional analysis), the participants with information on either depressive symptoms or glucose levels in at least one measurement point (2001, 2007, or 2012), and information on SES in 2001 were included ( $n = 2572$ ).



Individuals with Type 1 diabetes or Type 2 diabetes in 2001 were excluded ( $n = 23$ ).

Therefore, the analytic sample comprised 2549 participants (70.9% of the original sample).

The mediation analysis was conducted only in women. Those female participants who had information on at least one of the variables being a part of the tested model and who did not have the diagnosis of Type 1 diabetes or Type 2 diabetes in 2001 were included in this analysis ( $n = 1820$ ).

The attrition analysis, which were conducted using multilevel mixed-effects logistic regression (QR decomposition) with three measurement points, showed that higher glucose levels ( $OR = 18.57$ , 95% CI [4.42, 77.90],  $p < .001$ ), lower SES ( $OR = 2.45$ , 95% CI [1.84, 3.27],  $p < .001$ ), and female sex ( $OR = 3.97$ , 95% CI [2.95, 5.36],  $p < 0.001$ ) predicted greater drop-out. Older age was associated with lower attrition ( $OR = 0.94$ , 95% CI [0.91, 0.97],  $p < .001$ ). Higher depressive symptoms did not predict drop-out ( $OR = 1.07$ , 95% CI [0.86, 1.34],  $p = .54$ ). With regard to the pattern of missing values, 1934 (64.0%) participants had data on either depressive symptoms or glucose in all three waves, 284 (9.4%) in 2001, 272 (9.0%) in 2001 and 2007, 200 (6.6%) in 2007 and 2012, 137 (4.5%) in 2001 and 2012, 108 (3.6%) in 2007, and 89 (2.9%) in 2012.

## Measures

**Depressive symptoms.** Depressive symptoms were assessed in 2001, 2007, and 2012 using a modified version of the Beck Depression Inventory (BDI-I; Beck & Steer, 1987), which was translated into Finnish and adopted for use in the Cardiovascular Risk in Young Finns Study (Elovainio et al., 2015; Katainen, Raikkonen, Keskivaara, & Keltikangas-Jarvinen, 1999). The original version of the instrument consists of 21 items with four alternative response options for each item, representing increasing levels in the intensity of depressive symptoms, e.g., 0 = *I do not feel sad*, 1 = *I feel sad*, 2 = *I am sad all the time and I can't snap out of it*, and 3 = *I am so sad and unhappy that I can't stand it*. In the modified

version of the BDI-I, the participants are asked to rate the second mildest statement of each item of the original BDI-I (in the above example, this would be option 1 = *I feel sad*) on a 5-point Likert scale ranging from *totally disagree* (1) to *totally agree* (5). These second mildest statements were selected for the modified measure as they were expected to better capture a wider range of variation in milder depressive tendencies within the general population compared with the original version of the scale (Katainen, Räikkönen, & Keltikangas-Järvinen, 1999). They also made the inventory easier to fill out, and thus, less-time consuming (Katainen, Räikkönen, & Keltikangas-Järvinen, 1999), since the participants indicated their level of agreement with one statement instead of the need to review four separate statements of each item in order to choose one of them. A severity score of depressive symptoms was calculated as the mean score of responses. Internal consistency coefficient (Cronbach's  $\alpha$ ) as an indicator of reliability of the scale was .92 in 2001, and .93 in 2007 and 2012. The modified BDI-I has been shown to be correlated with the Beck Depression Inventory-II (BDI-II), a measure designed to screen for depressive disorder, with the coefficient .77 (Rosenström et al., 2012). The validity of the scale has also been demonstrated through its correlations with psychosocial characteristics known to be associated with depressive symptoms, including negative emotionality and low sociability (Katainen, Räikkönen, & Keltikangas-Järvinen, 1999), fatigability and sentimentality (Elovainio et al., 2004), hostility and low levels of perceived social support (Heponiemi et al., 2006), or emotional reactivity and perseveration (Hintsä et al., 2016).

**Fasting glucose.** Fasting serum glucose concentrations were measured in 2001, 2007, and 2012 with the enzymatic hexokinase method (Glucose reagent, Beckman Coulter Biomedical) using an Olympus AU400 instrument (Olympus, Tokyo, Japan). Due to the fact that the distribution of glucose levels was significantly skewed to the right (positive skewness), glucose values were log transformed in the main analysis.

**Potential confounders.** All the statistical analysis was adjusted for the potential, confounding effects of baseline age and SES as the two variables have been associated with both depressive symptoms and Type 2 diabetes (Everson, Maty, Lynch, & Kaplan, 2002; Sutin et al., 2013; Wild, Roglic, Green, Sicree, & King, 2004). SES was measured as an educational level. The categories were as follows: high (graduated from or studying at a university, or graduated from a polytechnic institution); intermediate (secondary education: a high school (three degrees) or a vocational school (three degrees) as the highest degree); and low (a primary school (nine degrees) or less as the highest level of education).

**Potential mediators.** Information on body fat, inflammation, alcohol consumption, and tobacco or cigarette smoking was collected in 2001 and 2007. Body mass index (BMI) was used as an indicator of body fat. It was calculated as  $\text{weight (kg)} / \text{height}^2 (\text{m}^2)$ . Height was measured with a wall-stated stadiometer and weight was measured with Seca scales. Inflammation was defined by levels of serum high-sensitivity C-reactive protein (hs-CRP), which were measured using an automated analyzer (Olympus AU400, Olympus, USA) and a highly sensitive turbidimetric immunoassay kit (CRP-UL-assay, Wako Chemicals, Neuss, Germany). The frequency of alcohol consumption was assessed with one question (number of occasions per week when at least six units of alcoholic beverages are consumed within one day) having six alternative responses (1 = *twice a week or more often*, 2 = *once a week*, 3 = *twice or three times a month*, 4 = *once a month*, 5 = *twice to six times a year*, and 6 = *rarely or never*). The frequency of current tobacco or cigarette smoking was measured by one question with five alternative answers (1 = *I smoke once a day or more often*, 2 = *I smoke once a week or more often but not every day*, 3 = *I smoke less than once a week*, 4 = *I quit smoking*, and 5 = *I have never smoked*). Alcohol intake and tobacco or cigarette smoking were recoded so that higher values indicated higher frequency.

## Statistical Analysis

To test the direction of the association between depressive symptoms and glucose levels in women and men, and to assess whether there would be sex differences in the obtained path coefficients, multiple-group cross-lagged path analysis in structural equation modeling (SEM) was performed (first, with data from 2001 and 2012, and then, additionally, with data from all the three measurement points, i.e., 2001, 2007, and 2012). Parallel multiple mediation in SEM was used to examine whether changes in BMI, hs-CRP, alcohol consumption, or tobacco or cigarette smoking (from 2001 to 2007) mediate the association between depressive symptoms (2001) and glucose levels (2012). The model was adjusted for baseline age and SES, and the baseline values of the mediators of interest and glucose levels. Indirect effects were tested by calculating confidence intervals (normal-based 95% CI) using bootstrapping with 1000 repetitions; this procedure has been recommended in assessing indirect effects in multiple mediator models (Preacher & Hayes, 2008).

Goodness-of-fit of the SEM models was evaluated based on: the chi-squared test ( $\chi^2$ ), the root mean squared error of approximation (RMSEA), the comparative fit index (CFI), and the Tucker-Lewis Index (TLI). A non-significant  $\chi^2$  value indicates that the model is a good fit to the data (Acock, 2013). This index is, however, highly sensitive to sample size, especially when the number of observations is greater than 200 (Hoe, 2008). RMSEA values of less than .05 and .08 indicate a good and a reasonable fit, respectively (Acock, 2013). Nevertheless, this measure has been shown to often falsely indicate poor fitting in models with small degrees of freedom, especially in those with a very small sample size (Kenny, Kaniskan, & McCoach, 2015). For CFI and TLI, values above .90 and .95 represent an acceptable and a good fit, respectively (Acock, 2013).

The comparison of the models with regard to their fit was conducted by computing the difference in  $\chi^2$  test ( $\Delta\chi^2$ ). If the  $\Delta\chi^2$  was significant at  $p < .05$  (Byrne, 2001), a model with

more freely estimated parameters was accepted as being a better fit to the data than a model in which fewer parameters were estimated.

To avoid biased results due to missing data, the main analyses were performed using the full information maximum likelihood estimation (FIML; Dong & Peng, 2013). In this approach, all available data (both from complete and incomplete cases) are utilized during parameter estimation. The FIML obtains parameter estimates by maximizing the likelihood function of the incomplete data. The method produces unbiased estimates when data are missing completely at random or missing at random. Due to the fact that this assumption is not testable, pattern mixture modeling (PMM) was applied to deal with non-ignorable (i.e., informative) drop-out (Dantan, Proust-Lima, Letenneur, & Jacqmin-Gadda, 2008). In this method, a covariate characterizing the participants' drop-out pattern is created and included in the analysis as a potentially confounding variable. The attrition indicator in the present study was based on the number of follow-ups in which the participant took part (i.e., had data on either depressive symptoms or glucose). Since this variable provided information for the purpose of missing at random estimation, the drop-out did not need to be ignorable. The moderating effect of the attrition indicator on the associations of interest was not included in the multiple-group cross-lagged models as neither interaction effect of the attrition indicator and glucose on depressive symptoms ( $p = .68$ ) nor interaction effect of the attrition indicator and depressive symptoms on glucose ( $p = .39$ ) was observed when fitting regression models to panel data ("xtreg").

The differences between women and men in the study variables were tested with the  $t$ -test and the Mann-Whitney  $U$  test. All the statistical analyses were performed using STATA/SE 13 software.

## Results

Table 1 shows the characteristics of the participants included in the first part of the statistical analysis (multiple-group cross-lagged analysis with two measurement points). In 2001, women had higher SES and scored higher than men on depressive symptoms. Compared with women, men had higher glucose concentrations in 2001 and 2012. Women and men did not differ in age and depressive symptoms measured in 2012.

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Insert Table 1 here  
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In the model adjusted for baseline age and SES, equality constraints were imposed on paths that were not statistically different between women and men (i.e., paths b and d,  $p$ s > .05; Figure 1). The model fit difference between this model and the saturated unconstrained model (with all coefficients allowed to vary across sex) was non-significant ( $\Delta\chi^2(2) = 0.28$ ,  $p = .87$ ), suggesting that the former (i.e., more parsimonious) should be retained. When the retained model and the fully constrained model were compared, the model fit difference was significant ( $\Delta\chi^2(2) = 9.94$ ,  $p = .007$ ), which indicated that the partially constrained model (i.e., less parsimonious) should be selected.

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Insert Figure 1 here  
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Figure 1 and Table 2 present the results of the final model. The model was a good fit to the data ( $\chi^2(2) = 0.28$ , RMSEA = .00, CFI = 1.00, TLI = 1.01). Depressive symptoms predicted glucose levels in women ( $\beta = .07$ ,  $p = .023$ ) but not in men ( $\beta = -.03$ ,  $p = .45$ ). This sex difference was statistically significant ( $p = .042$ ). Glucose levels, however, did not predict subsequent depressive symptoms in either women ( $\beta = .00$ ,  $p = .96$ ) or men ( $\beta = .00$ ,  $p = .96$ ).

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Insert Table 2 here  
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Additionally, multiple-group cross-lagged analysis with three measurement points controlling for baseline age and SES was performed. The model in which all the paths were allowed to vary across sex did not provide a satisfactory fit to the data ( $\chi^2(8) = 154.61$ , RMSEA = .12, CFI = .95, TLI = 0.83). To significantly improve the fit, a correlation between depressive symptoms in 2001 and depressive symptoms in 2012 (path l) was added to the equation ( $\chi^2(6) = 52.62$ , RMSEA = .08, CFI = .99, TLI = 0.93; Figure 2). This model showed that only paths b and c were statistically different between women and men ( $ps < .05$ ). Further, path e was found to be significant in women but not in men, although this difference was non-significant ( $p > .05$ ). When equality constraints were imposed on all the paths except paths b, c, and e, the model fit difference between this new model ( $\chi^2(14) = 67.13$ , RMSEA = .06, CFI = .98, TLI = 0.97) and the fully unconstrained model was non-significant ( $\Delta\chi^2(8) = 14.51$ ,  $p = .069$ ). Thus, the model with equality constraints (i.e., more parsimonious) was selected. Thereafter, the model fit difference between this partially constrained model and a fully constrained model was tested. The results showed that the difference was significant ( $\Delta\chi^2(3) = 13.15$ ,  $p = .004$ ), suggesting that the former model should be retained.

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Insert Figure 2 here  
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The results of the final model are shown in Figure 2 and Supplemental Table 1. Depressive symptoms in 2001 predicted glucose levels in 2007 in women ( $\beta = .06$ ,  $p = .027$ ) but not in men ( $\beta = .02$ ,  $p = .61$ ). As above-mentioned, this sex difference was non-significant ( $p = .32$ ). There was no association going from depressive symptoms in 2007 to glucose

concentrations in 2012 in either women ( $\beta = -.01, p = .56$ ) or men ( $\beta = -.01, p = .56$ ).

Furthermore, glucose levels did not predict depressive symptoms in either sex (years 2001-2007:  $\beta = .01, p = .51$  in women and  $\beta = .01, p = .51$  in men; years 2007-2012:  $\beta = .02, p = .42$  in women and  $\beta = .01, p = .42$  in men).

### **Mediation analysis**

Further analysis was performed only in women among whom the association from depressive symptoms to glucose levels was found. Descriptive statistics of the female participants included in this analysis are presented in Supplemental Table 2. The results of the parallel multiple mediation adjusted for baseline age and SES, and the baseline scores of the tested mediators and glucose levels are presented in Table 3. The model was a good fit to the data ( $\chi^2(22) = 193.99$ , RMSEA = .07, CFI = .95, TLI = 0.89). Neither the total indirect effect ( $\beta = .01, b = 0.00$ , 95% CI [-0.00, 0.01],  $p = .13$ ) nor the specific indirect effects (BMI:  $\beta = .01, b = 0.00$ , 95% CI [-0.00, 0.00],  $p = .15$ ; hs-CRP:  $\beta = -.00, b = -0.00$ , 95% CI [-0.00, 0.00],  $p = .83$ ; alcohol intake:  $\beta = .00, b = 0.00$ , 95% CI [-0.00, 0.00],  $p = .46$ ; and tobacco or cigarette smoking:  $\beta = .00, b = 0.00$ , 95% CI [-0.00, 0.00],  $p = .85$ ) were statistically significant.

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Insert Table 3 here  
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### **Discussion**

To our knowledge, this is the first study, which examined a bidirectional association between depressive symptoms and glucose concentrations in women and men, and the factors mediating this relationship. First, the results from our prospective, population-based, cohort study showed that depressive symptoms in 2001 were positively associated with glucose levels in 2007 and 2012 in women but not in men. Depressive symptoms in 2007 did not,



however, predict glucose concentrations in 2012 in either sex. Thus, it is possible that the experience of depressive symptoms especially at the beginning of the fourth decade of life may be an important risk factor for the development of Type 2 diabetes in women. Further, the observed sex difference in the association going from depressive symptoms to glucose levels reached statistical significance within an 11- but not a 6-year time lag, suggesting that the difference between women and men in this relationship may develop over a longer time period. The study also found that glucose levels in 2001 did not predict depressive symptoms in 2007 or 2012 and that glucose concentrations in 2007 were not associated with depressive symptoms in 2012 in either women or men. Moreover, depressive symptoms and glucose levels were shown to be moderately stable over time, which could be driven by the influence of genetic factors and the relative stability of demographic, lifestyle, and environmental factors, such as socioeconomic position (Carvalho, 2012), dietary patterns (Johns et al., 2014), or physical activity (Telama et al., 2014). Finally, our findings suggested that the association from depressive symptoms to glucose levels may not be mediated by changes in BMI, hs-CRP, alcohol intake, or tobacco or cigarette smoking.

Contrary to the conclusion of the latest literature review (Tabák et al., 2014), our study supported the notion that symptoms of depression can directly increase the risk of Type 2 diabetes by showing that depressive symptoms were positively associated with glucose levels. As changes in hs-CRP did not mediate the studied association, chronic inflammation is unlikely to be a mechanism underlying the direct effect of depressive symptoms on disturbed glucose homeostasis. It is, however, possible that biological changes induced by depressive symptoms, such as dysfunctions in the HPA axis and the SNS, which were not examined in the present study, could play a mediating role in the link between depressive symptoms and hyperglycemia.

Moreover, our research showed that the association between depressive symptoms and glucose concentrations was not mediated by changes in BMI, alcohol intake, or tobacco or cigarette smoking. This is not in line with the results of a previous study (Chiu, Wray, Beverly, & Dominic, 2010), which suggested that depressive symptoms may affect glycemia indirectly by changes in BMI and smoking. Given, however, that this study did not control for the baseline values of glucose levels and was based on a clinical sample of individuals diagnosed with Type 2 diabetes, the full causal pathways linking depressive symptoms to hyperglycemia could not have been established. Thus, our investigation added considerably to the current evidence base.

In our study, the association going from depressive symptoms to glucose concentrations was observed in women but not in men. These results are in agreement with the finding from cross-sectional research of the Hoorn Study (Adriaanse et al., 2008), which suggested a sex interaction, with an enhanced risk of prediabetes and Type 2 diabetes in depressed women but not in men. In contrast to the present investigation, a Swedish longitudinal, population-based study (Eriksson et al., 2008) documented an increased risk of prediabetes and Type 2 diabetes in men with psychological distress (i.e., symptoms of anxiety, apathy, depression, fatigue, and insomnia) but not in women (except for prediabetes in the middle index group of distress). This inconsistency could result from the fact that the measure of distress in the Swedish study consisted of only five items, suggesting low reliability of the instrument.

Sex differences in coping mechanisms in response to stress/depressive symptoms could be one of the plausible explanations for the presence of the positive association between depressive symptoms and glucose levels in women but not in men. Women and men have been shown to differ in styles of coping with distress (Mikolajczyk, El Ansari, & Maxwell, 2009; Piccinelli & Wilkinson, 2000; Tamres, Janicki, & Helgeson, 2002) that might contribute to differential diabetes risk factors. For example, men have a tendency to engage in

physical and instrumental activities to overcome their depressed mood, whereas women tend to become less physically active and engage in more ruminative thinking (Piccinelli & Wilkinson, 2000; Tamres et al., 2002) that maintains their depressive state (Nolen-Hoeksema, 2000). In addition, stress and depressive symptoms may lead to the adoption of an unhealthy diet (i.e., more frequent consumption of sweets/fast food and less frequent consumption of fruits and vegetables) in women but not in men (Mikolajczyk et al., 2009). These sex differences in adherence to exercise and healthy diet could further result in an increased risk for the development of Type 2 diabetes (Alhazmi et al., 2014; Jeon et al., 2007) among women but not among men.

The present study supports the conclusion of a recent literature review (Tabák et al., 2014) that pathophysiological changes associated with Type 2 diabetes, including increased glucose concentrations, might not cause depressive symptoms. Our findings are also consistent with the results of the Whitehall II Study (Akbaraly et al., 2013), which showed that elevated fasting glucose levels (treated as a continuous variable) do not increase the risk depressive symptoms in either sex. Additionally, in line with the present findings, the U.S. Multi-Ethnic Study of Atherosclerosis (Golden et al., 2008) found an increased risk of depressive symptoms in individuals with treated Type 2 diabetes—but a decreased risk in those with prediabetes and untreated Type 2 diabetes (prediabetes and diabetes status was defined by fasting glucose concentrations), providing evidence that chronically elevated glucose levels may not contribute to depressive symptoms. However, our results are not in accordance with the findings from the English Longitudinal Study of Aging (Hamer et al., 2011), which revealed that elevated glucose levels (indicated by a measure of glycated hemoglobin, HbA<sub>1C</sub>) can increase the risk of depressive symptoms, especially in men. The discrepancy might be due to different methods used to measure glucose concentrations, since the same study also found that Type 2 diabetes (when defined using both HbA<sub>1C</sub> and fasting

glucose), and prediabetes (when defined using HbA<sub>1C</sub> but not fasting glucose) are associated with an increased risk of depressive symptoms. Similarly, cross-sectional data from the Hertfordshire Cohort Study (Holt et al., 2009) showed a positive association of depressive symptoms with glycemia in women and men when glucose concentrations were measured with 2-hour post-load glucose but not with fasting glucose.

Some methodological limitations of our study need to be taken into account when interpreting the results. First, depressive symptoms were self-reported, therefore some reporting bias could occur. Second, the present study did not sample clinically depressed individuals but people with depressive symptoms in the general population. Therefore, future studies need to focus on testing the association of glucose levels with clinically diagnosed depression in order to replicate our findings. Third, the study was based on a relatively young population (age range of 35 to 50 years in the latest follow-up,  $M = 42.54$ ). Given that the number of people diagnosed with Type 2 diabetes starts to increase rapidly in midlife (Wild et al., 2004), it is possible that our results provided an underestimate of the magnitude of the association between depressive symptoms and glucose levels among older people. Thus, it is advisable that the present study is reproduced in older populations. Further, the measurement of glucose concentrations was based on a single test of fasting glucose. Since there is some evidence which suggests that fasting glucose may be a less robust and reliable diagnostic tool for Type 2 diabetes than 2-hour post-load glucose (Pomerleau, McKeigue, & Chaturvedi, 1999) or HbA<sub>1C</sub> (Bonora & Tuomilehto, 2011), we recommend that future research could incorporate these two other measures of glycemia, in addition to fasting glucose, to verify our findings. Moreover, BMI might not have accurately reflected the changes in body fat of our participants. Research using more direct measures of adiposity is warranted to confirm that overweight or obesity are unlikely to mediate the association between depressive symptoms and hyperglycemia. In addition, our investigation did not take into account cumulative

exposure to excess body fat, inflammation, or health-risk behaviors, therefore the mediating role of these factors might have been underestimated. In further studies, this aspect is important to be considered. Finally, the potential mediating effect of dietary patterns and physical activity on the association between depressive symptoms and glucose levels was not tested in the present research. Thus, future studies are needed to examine the role of those factors in the relationship of interest.

The present study has a number of strengths. The inclusion of a young population can be seen not only as a limitation but also as a strength. Knowledge about whether depressive symptoms predict glucose concentrations before the peak age of the onset for Type 2 diabetes is valuable for better understanding the temporal course of the development of diabetes, and thus, for assuring the timely implementation of appropriate preventive interventions for this disease. Most previous studies of the association between depressive symptoms and glucose levels were conducted on older populations, therefore our study makes an important contribution to this field of research. Further, the use of three repeated measurements of depressive symptoms and fasting glucose, treated as continuous variables, over a long period of time (i.e., 11 years) and within the same population-based and large sample enabled to make more precise inference about the direction of the association between depressive symptoms and glucose levels. Moreover, the analysis was performed considering sex-specific differences. The current study also explored the mediating factors of the association from depressive symptoms to glucose levels. Finally, the use of the FIML estimation helped to produce results that are unlikely to be biased by attrition.

### **Conclusions**

The results showed that there is a positive association between depressive symptoms and glucose levels in women but not in men. The direction of this relationship seems to be from depressive symptoms to glucose levels rather than the reverse. Furthermore, the effect of

depressive symptoms on glucose levels may not be mediated by changes in body fat, inflammation, alcohol intake, or cigarette or tobacco smoking. Given this, health care professionals should be aware that women with elevated depressive symptoms may have elevated glucose levels, and thus may be at elevated risk for developing Type 2 diabetes. Future studies, in particular randomized clinical trials, are needed to assess whether the initiation of routine screening for depressive symptoms (which can include referral to mental health specialists) among women already at the beginning of the fourth decade of life could be of value in preventing glucose abnormalities.

The present results do not exclude the possibility that the association in the direction of Type 2 diabetes leading to depressive symptoms can be attributable to psychosocial stress caused by the diagnosis of Type 2 diabetes, the burden of treatment, and complications related to this disease (Tabák et al., 2014). Thus, routine screening for depressive symptoms in all patients diagnosed with Type 2 diabetes, as recommended by the American Association of Clinical Endocrinologists (Handelsman et al., 2015) and the Canadian Diabetes Association (Robinson, Luthra, & Vallis, 2013), should continue to be performed.

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Table 1

*Characteristics of the Study Participants by Sex*

| Study variables             | Women        |                        | Men          |                        | <i>p</i> -value for a difference |
|-----------------------------|--------------|------------------------|--------------|------------------------|----------------------------------|
|                             | <i>n</i> (%) | <i>M</i> ( <i>SD</i> ) | <i>n</i> (%) | <i>M</i> ( <i>SD</i> ) |                                  |
| Sex                         | 1406 (55.5)  |                        | 1128 (44.5)  |                        |                                  |
| Age in 2001 (years)         | 1406         | 31.53 (4.97)           | 1128         | 31.55 (5.00)           | .91                              |
| SES in 2001                 | 1406         |                        | 1128         |                        | .063                             |
| Low                         | 126 (9.0)    |                        | 97 (8.6)     |                        |                                  |
| Intermediate                | 885 (62.9)   |                        | 762 (67.6)   |                        |                                  |
| High                        | 395 (28.1)   |                        | 269 (23.9)   |                        |                                  |
| Depressive symptoms in 2001 | 1152         | 2.16 (0.66)            | 823          | 2.01 (0.58)            | < .001                           |

|  |      |             |      |             |        |
|--|------|-------------|------|-------------|--------|
| Depressive symptoms in 2007 <sup>a</sup> | 1090 | 2.13 (0.65) | 722  | 2.02 (0.59) | < .001 |
| Depressive symptoms in 2012              | 913  | 2.08 (0.64) | 627  | 2.05 (0.63) | .39    |
| Glucose in 2001 (mmol/l)                 | 1242 | 4.87 (0.44) | 1007 | 5.15 (0.42) | < .001 |
| Glucose in 2007 (mmol/l) <sup>b</sup>    | 1093 | 5.15 (0.59) | 843  | 5.43 (0.51) | < .001 |
| Glucose in 2012 (mmol/l)                 | 1002 | 5.22 (0.77) | 785  | 5.50 (0.70) | < .001 |

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*Note.* *M* = mean; *n* = number of participants; *SD* = standard deviation.

<sup>a, b</sup>The variable used in the cross-lagged model with three measurement points.

Table 2

*The Results of the Multiple-Group Cross-Lagged Analysis With Two Measurement Points (2001 and 2012) Testing for Sex Differences in the Association Between Depressive Symptoms and Glucose Levels (n = 2534)*

|                          | Women      |               |                 | Men        |               |                 |                                  |
|--------------------------|------------|---------------|-----------------|------------|---------------|-----------------|----------------------------------|
|                          | (n = 1406) |               |                 | (n = 1128) |               |                 |                                  |
|                          | <i>b</i>   | 95% CI        | <i>p</i> -value | <i>b</i>   | 95% CI        | <i>p</i> -value | <i>p</i> -value for a difference |
| Depressive symptoms 2012 |            |               |                 |            |               |                 |                                  |
| Depressive symptoms 2001 | 0.57       | [0.52, 0.62]  | < .001          | 0.68       | [0.61, 0.75]  | < .001          | .015                             |
| Glucose 2001             | 0.01       | [-0.32, 0.34] | .96             | 0.01       | [-0.32, 0.34] | .96             | -                                |
| Glucose 2012             |            |               |                 |            |               |                 |                                  |
| Glucose 2001             | 0.52       | [0.46, 0.58]  | < .001          | 0.52       | [0.46, 0.58]  | < .001          | -                                |
| Depressive symptoms 2001 | 0.01       | [0.00, 0.02]  | .024            | -0.00      | [-0.02, 0.01] | .45             | .042                             |

Table 3

| Outcome                               | Direct effect |                 | Indirect effect |                 | Total effect |                 |
|---------------------------------------|---------------|-----------------|-----------------|-----------------|--------------|-----------------|
|                                       | $\beta$       | <i>p</i> -value | $\beta$         | <i>p</i> -value | $\beta$      | <i>p</i> -value |
| <b>BMI</b>                            |               |                 |                 |                 |              |                 |
| Depressive symptoms -> BMI            | .03           | .13             |                 |                 | .03          | .13             |
| <b>hs-CRP</b>                         |               |                 |                 |                 |              |                 |
| Depressive symptoms -> hs-CRP         | -.01          | .81             |                 |                 | -.01         | .81             |
| <b>Alcohol intake</b>                 |               |                 |                 |                 |              |                 |
| Depressive symptoms -> Alcohol intake | .02           | .43             |                 |                 | .02          | .43             |
| <b>Tobacco or cigarette smoking</b>   |               |                 |                 |                 |              |                 |
| Depressive symptoms -> Smoking        | .02           | .30             |                 |                 | .02          | .30             |
| <b>Glucose</b>                        |               |                 |                 |                 |              |                 |

|   |     |        |      |     |     |        |
|---|-----|--------|------|-----|-----|--------|
| Depressive symptoms -> Glucose <sup>a</sup>                   | .04 | .21    | .01  | .13 | .05 | .12    |
| Depressive symptoms -> BMI -> Glucose <sup>b</sup>            |     |        | .01  | .15 |     |        |
| Depressive symptoms -> hs-CRP -> Glucose <sup>c</sup>         |     |        | -.00 | .83 |     |        |
| Depressive symptoms -> Alcohol intake -> Glucose <sup>d</sup> |     |        | .00  | .46 |     |        |
| Depressive symptoms -> Smoking -> Glucose <sup>e</sup>        |     |        | .00  | .85 |     |        |
| BMI -> Glucose  | .39 | < .001 |      |     | .39 | < .001 |
| hs-CRP -> Glucose   | .03 | .44    |      |     | .03 | .44    |
| Alcohol intake -> Glucose                                     | .08 | .025   |      |     | .08 | .025   |
| Tobacco or cigarette smoking -> Glucose                       | .01 | .85    |      |     | .01 | .85    |

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*Note.*  $\beta$  = standardized linear regression coefficient. The model fitted with logarithmically transformed glucose values and adjusted for baseline: age, SES, BMI, hs-CRP, alcohol intake, tobacco or cigarette smoking, and glucose.

<sup>a</sup>The total of the indirect effects. <sup>b-e</sup>The specific indirect effects.

